Research Submissions

Low-Dose Tizanidine With Nonsteroidal Anti-inflammatory Drugs for Detoxification From Analgesic Rebound Headache

Timothy R. Smith, MD, RPh

Objective.—To describe an outpatient regimen for analgesic detoxification and resolution of analgesic rebound headache.

Background.—Frequent analgesic use is believed to promote the transformation of episodic migraine into a chronic, pervasive headache syndrome. Management of pain precipitated by analgesic withdrawal is crucial to treatment success. Outpatient treatment protocols designed to achieve successful withdrawal will reduce costs and potentially lead to more widespread implementation of therapy.

Methods.—Patients with appropriate histories were managed on an outpatient basis for detoxification by discontinuation of the offending analgesic and initiation of treatment with tizanidine and a long-acting nonsteroidal anti-inflammatory drug. Patients kept diaries of pain and medication use. Results were evaluated at 6 and 12 weeks. Patients able to tolerate no or trivial analgesic use (ie, 4 or fewer doses in each 2-week period) were considered responders.

Results.—At 6 weeks, 36 patients (65%) were responders. At 12 weeks, 38 patients (69%) were responders. The chronic daily headache pattern had resolved at 12 weeks in 34 patients (62%).

Conclusions.—This treatment protocol was well tolerated and yielded a high degree of efficacy, demonstrating that outpatient management can be effective for achieving analgesic withdrawal and resolution of analgesic rebound headache.

Key words: chronic daily headache, analgesic rebound headache, transformed migraine, tizanidine, Zanaflex

Abbreviations: CDH chronic daily headache, ARH analgesic rebound headache, NSAID nonsteroidal anti-inflammatory drug, DHE dihydroergotamine

(*Headache.* 2002;42:175-177)

Patients with migraine are at risk for transformation of their headaches into a chronic daily headache (CDH) pattern. More than 80% of patients with transformed migraine have a history of frequent use of analgesic medications, and are considered to have analgesic rebound headache (ARH), a CDH syndrome whose resolution typically requires intensive therapeutic intervention.[1] Most patients with ARH revert to intermittent migraine attacks if the contributing analgesics can be withheld for a sufficient period of time, usually 8 to 12 weeks or longer.[1-3] Because of the patient's "rebound" pain, however, successful detoxification from symptomatic medication is frequently difficult. Assisting patients in management of their analgesic rebound head pain during the transition period is crucial to treatment success.

Around-the-clock intravenous administration of dihydroergotamine (DHE) has been used successfully as a "bridge" to detoxification, both on an inpatient basis and an outpatient basis at infusion centers.[4,5] Investigators have reported the use of other agents to bridge the patient through detoxification, such as short-term daily administration of sumatriptan.[3] Such programs have been successful with some patients, but they are expensive and somewhat controversial.

Structurally similar to clonidine, tizanidine acts by α_2 agonism at polysynaptic central nervous system

From Mercy Health Research and Ryan Headache Center, St. Louis, Mo.

Address all correspondence to Dr. Timothy R. Smith, Mercy Health Research and Ryan Headache Center, Suite 200, 1585 Woodlake Drive, St. Louis, MO 63017.

Accepted for publication November 16, 2001.

pathways to reduce muscle tone associated with spasticity.[6] Many neurologists and headache specialists have moved to incorporating tizanidine into rational polypharmacy protocols for treatment of difficult headache syndromes. Small studies and case reports provided some preliminary basis for such treatment.[7,8]

This article is the first published report on the use of low-dose tizanidine for detoxification and resolution of ARH.

METHODS

Mercy Health Research/Ryan Headache Center is a research institute and headache clinic affiliated with Mercy Health, an integrated health system serving the St. Louis, Missouri area. We reviewed the charts of 87 patients with a history of medication overuse and transformed migraine who were evaluated at the center between October 1, 1998 and October 31, 1999. The patients were instructed to abruptly discontinue frequent use (ie, multiple daily doses 5 to 7 days per week) of all analgesics and were treated on an outpatient basis during detoxification. Specific patient education materials regarding ARH and frequent clinic visits supplemented pharmacotherapy. Patients kept diaries of their use of the study medication and other analgesics, pain, and adverse events. The diaries were returned and incorporated into their medical charts. Treatment effectiveness was assessed by review of the charts and study diaries at 6 and 12 weeks following the patient's final dose of analgesics.

A subset of 55 patients who received low-dose tizanidine in conjunction with a daily long-acting nonsteroidal anti-inflammatory drug (NSAID) were examined for the purposes of this report. The tizanidine/NSAID regimen was started on the same day as abrupt withdrawal of analgesic medications. All patients began tizanidine at a dosage of 2 mg at bedtime, and the dose was titrated upwards by 2 mg every 3 to 5 days until a therapeutic effect was achieved or sedation occurred. The tizanidine dosage range was 2 to 16 mg daily (average 3.6 mg) usually taken as a single dose at bedtime. The NSAID (piroxicam, rofecoxib, naproxyn, ketoprofen SR, or celecoxib) was usually taken in the morning. During the treatment period, patients relieved severe head pain by self-administration of DHE or a triptan (sumatriptan, rizatriptan, or zolmitriptan), as needed. In 4 patients who had been using triptan drugs frequently, only DHE was allowed for acute migraine treatment.

Patients with no or trivial analgesic use (ie, 4 or fewer doses in each 2-week period of acetylsalicylic acid [ASA], acetaminophen [APAP], ASA-APAP-caffeine, butalbital compound, ibuprofen and/or propoxyphene compound) at 6 weeks and 12 weeks were considered "responders." Those who continued frequent analgesic use were considered "nonresponders." Evidence of resolution of CDH (ie, headache frequency reduced to less than 15 days per month) was assessed at 12 weeks.

RESULTS

Forty-six (84%) of the patients were women and 9 (16%) were men. The average age was 40.5 years (range, 19 to 72 years).

Evaluable results were obtained for 53 of 55 patients. Two patients did not return any of their diaries and were lost to follow-up before the 6-week evaluation; they were included in the data analysis as nonresponders.

Treatment-limiting side effects were infrequent, occurring in 3 (5%) of 55 patients. Excessive drowsiness was the major complaint in 2 of the 3, 1 of whom was receiving 4 mg daily of tizanidine and the other 6 mg daily. The third patient complained of vivid dreams. All 3 remained under the care of the investigator and were included in the analysis as nonresponders.

At 6 weeks, 36 patients (65%) were responders, and 19 (35%) were nonresponders, including the 2 patients lost to follow-up and the 3 who experienced treatment-limiting side effects. At 12 weeks, 38 patients (69%) were responders, and 17 (31%) were nonresponders. All 4 patients with triptan overuse were responders by 12 weeks. Chronic daily headache patterns had resolved in 34 patients (62%) at 12 weeks; 21 (38%) experienced no resolution, but 4 of them had maintained their cessation of frequent analgesic use. After 12 weeks, all responders were able to discontinue the NSAID used in treatment without worsening of their headaches. At the end of 12 weeks, all responding patients continued to use triptans or DHE as abortive therapy for intermittent migraine attacks.

COMMENTS

In this group of patients, the combination of low-dose tizanidine with a long-acting NSAID was useful in the treatment of ARH as a supportive therapy during the period of analgesic withdrawal. The treatment was well tolerated and exhibited a reasonably high degree of efficacy. Tizanidine use frequently is complicated by somnolence (up to 48%) and dry mouth (up to 49%).[6] In contrast, the patients in this study reported very few and mild side effects, presumably because the dose was relatively low and taken at bedtime. The treatment response rate of 69% compares well with results reported by Drucker and Tepper in their small, open-label, prospective study of outpatient treatment with sumatriptan daily for up to 10 days during analgesic withdrawal (58% at 1 month and 69% at 6 months).[3] All but 2 of those classified as responders at the end of our study had responded by 6 weeks, suggesting that most patients who will benefit from this treatment will do so relatively quickly.

Cost containment is an important consideration in the assessment of any treatment protocol. In previous studies of ARH management, Raskin, Silberstein et al, and Rapoport have reported 89% to 92% response rates achieved with repetitive intravenous DHE, but such treatment requires a concentrated and expensive utilization of medical resources.[4,5,9] Both the study by Drucker and Tepper and the present study were conducted on an outpatient basis, and both achieved respectable treatment response rates, and the latter did not require daily administration of a triptan.

The combination of tizanidine with an anti-inflammatory agent may provide protection against the exacerbation of head pain through multiple mechanisms that are likely to be additive. The agonism of α_2 receptors at spinal interneurons and centrally in the locus ceruleus down-regulates the quantity of sympathetic amines present in the synaptic spaces and thus possibly decreases central nervous system hyperexcitability.[6] The skeletal muscle relaxant, antinociceptive, and hypnotic effects of tizanidine may contribute to that effect as well, and the antiprostaglandin effects of the long-acting NSAIDs provide pain relief while appearing not to promote analgesic rebound.[10]

Randomized, placebo-controlled, double-blind studies will be required to better define the utility of the combination of low-dose tizanidine and NSAIDs for the treatment of ARH. A recent open-label, two-center, dose-titration study by Saper and colleagues has provided preliminary support for the efficacy, safety, and tolerability of tizanidine in the prophylaxis of CDHs in patients without ARH, and a multicenter, double-blind, placebo-controlled safety and efficacy study of tizanidine for CDH is in progress.[11] Tizanidine ultimately may play a role both in the treatment of CDH and in detoxification of patients with ARH.

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